EXHIBIT 21

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UNITED STATES DISTRICT COURT
CENTRAL DISTRICT OF CALIFORNIA
WESTERN DIVISION

CENTOCOR, INC. Plaintiff, v. GENENTECH, INC. and CITY OF HOPE NATIONAL MEDICAL CENTER Defendants.	Case No. CV 08-03573 MRP (CTx) The Honorable Marianna R. Pfaelzer **CENTOCOR, INC.'S OPENING BRIEF ON CLAIM CONSTRUCTION** Date: May 12, 2009 Time: 10:00 a.m. Place: Courtroom 12

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I. INTRODUCTION

The parties seek the Court's construction of claim terms in two patents, U.S. Patent 6,331,415 (Cabilly II Patent) and U.S. Patent 6,417,335 (335 Patent).

A. Cabilly Patent Family History

For the second time, this Court faces claim construction issues posed by the Cabilly II Patent. Unlike Genentech's shifting positions – even after extensive litigation in *MedImmune, Inc. v. Genentech, Inc. and City of Hope*, Case No. CV 03-02567 – Centocor's proposed claim constructions in this case largely reflect the Court's prior *Markman* Order in *MedImmune*. *See* August 16, 2007 Order, Docket No. 243 (*MedImmune* Op.). Centocor only diverges from the *MedImmune* constructions on one term, "produced as separate molecules in a single host cell," where it provides new evidence and case law and urges the Court to reconsider its previous decision.

The Cabilly family, as the Court is aware, has a long and tortured history in the Patent and Trademark Office (PTO) and in the federal courts, dating back a quarter century to 1983, when the first application was filed. The Cabilly I patent issued twenty years ago, in 1989, and expired in 2006. (Ex. A).[1] As Genentech and City of Hope acknowledge (Defendants' Opening Brief ("Br.") at 2), for years Centocor paid royalties in the hundreds of millions of dollars under license agreements to the Cabilly I patent (as did other industry members like MedImmune). Cabilly I was set to expire in 2006 and the industry expected that the natural life of the Cabilly invention would end at that time.

However, this Court's *MedImmune* opinion summarizes well what happened next. At the time Cabilly I issued, Genentech had a continuation pending. On the same day that Cabilly I issued, a separate patent owned by a British company, Celltech R&D, Ltd., issued. This patent, the "Boss Patent" (U.S. Patent 4,816,397)

[1] All references to "Ex. __" refer to the exhibits attached to the Declaration of Amanda M. Kessel, contemporaneously submitted, unless otherwise stated.

would have expired in 2006, on the same day as Cabilly I. (Ex. B). This did not come to pass. Genentech copied claims from the Boss Patent into its own continuation application to provoke an interference to determine whether Cabilly or Boss was the first to invent the purported invention. After years of winding through the PTO, the PTO eventually awarded priority to Boss, concluding that Cabilly was not entitled to a patent. *MedImmune* Op. at 3.

Undeterred, Genentech started a challenge to that decision in the federal courts. Ultimately, Genentech and Celltech brokered a deal that would vacate the PTO's priority determination, revoke the Boss patent, and allow the Cabilly II application to issue as a patent. *Id*. Cabilly II issued in December 2001 and will not expire until 2018. *See* Ex. C. Thus, the practical effect of the private agreement between Genentech and Celltech is to extend the term of patent protection (and royalties collected) by over a decade. Cabilly I expired, and the revoked Boss patent would have expired, in 2006. Cabilly II will not expire until 2018.

Even today, Cabilly II's unusual history in the PTO continues. Starting in 2005, the PTO took up two reexamination challenges to the Cabilly II Patent. For years, throughout numerous office actions, the PTO rejected all of Cabilly II's claims as invalid, primarily in light of the Cabilly I Patent. In a surprising recent move, following a series of *ex parte* interviews with Genentech, the PTO reversed course and issued a Notice of Intent to Issue Reexamination Certificate, finding the Cabilly II claims patentable, even though these claims had stood rejected for over two years. *See* Sernel Decl. Ex. L, Doc. 79.

B. The Cabilly II Claim Construction Issues

The claim construction issues posed in this case face the same tension this court recognized in its *MedImmune* opinion – a tension stemming from the fact that the asserted claims were not written by Cabilly, but by Boss, and were copied into Cabilly II for the purpose of provoking an interference proceeding:

> A specification written by Dr. Cabilly, whose research involved bacteria, has been combined with claim language written by Dr. Boss, whose research involved yeast. . . . there appears not to have been one 'true intent' behind this patent for the Court to discern and use as its touchstone.

Op. at 12.

With its proposed claim construction, Genentech attempts to expand the scope of its claims to cover something that it did not invent, describe, or teach. Centocor simply seeks claim constructions that reflect the proper scope of what Cabilly invented: "The role [of claim construction] is neither to limit nor broaden the claims, but to define, as a matter of law, the invention that has been patented." *Netword, LLC v. Centraal Corp.*, 242 F.3d 1347, 1352 (Fed. Cir. 2001). The Federal Circuit recently affirmed the importance of this mandate in its *Ariad Pharms., Inc. v. Eli Lilly & Co.* decision commenting that if "a court would properly interpret … claim[s] as limited" to what is described and taught in the specification, then the claims would not suffer from critical validity flaws. 2009 U.S. App. LEXIS 6915 at *25-26 (Fed. Cir. Apr. 3, 2009) (Ex. D).

In this case, the Court is being asked to construe the following terms from the Cabilly II Patent:

- **"Vector"** Centocor asks the Court to follow its prior, well-reasoned construction in *MedImmune*.
- **"Transformed host cell"** Centocor asks the Court to construe this term consistent with the construction Genentech agreed to in *MedImmune*.
- **"Transformed host cell comprising at least two vectors"** Centocor asks the Court to construe this phrase as a logical combination of the terms "transformed host cell" and "vector."
- **"Immunoglobulin" and "immunoglobulin molecule"** Centocor asks the Court to construe these terms consistent with the agreed-upon construction of "immunoglobulin" in *MedImmune*.
- **"Produced as separate molecules in a single host cell"** Centocor asks

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the Court to revisit its construction of this term in *MedImmune*.

- **"Immunologically functional immunoglobulin fragment" and "variable domain"** There is no dispute.

C. The 335 Patent Claim Construction Issues

Genentech responded to Centocor's Cabilly II declaratory judgment action by counterclaiming on patents of its own, only one of which Genentech says it will continue to assert. That patent, the 335 Patent, is a narrow patent directed to loading a specific numerical ratio of antibody to resin in a cation exchange chromatography column used in a process for purifying antibodies. (Ex. E). The claim construction issues for that patent arise from the fact that, in three of the four asserted claims, the claimed numerical ratio is preceded by the modifier "about." Centocor proposes that "about" be construed in accordance with its natural meaning, in light of the directives in the 335 Patent's specification and prosecution history. Genentech's position, that "about" needs no construction, would leave the claim boundaries entirely free-form and undefined.

II. GENERAL PRINCIPLES GOVERNING CLAIM CONSTRUCTION

The principles of claim construction are well known. "[T]he construction of a patent, including terms of art within its claim, is exclusively within the providence of the court." *Markman v. Westview Instruments*, 517 U.S. 370, 372 (1996). "The words of a [patent] claim are generally given their ordinary and customary meaning, " which is "the meaning that the term would have to a person of ordinary skill in the art in question…as of the [patent's] effective filing date." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc). In interpreting a claim, "the court should first look to the intrinsic evidence of record, i.e. the patent itself, including the claims, the specification, and if in evidence, the prosecution history." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The patent specification "is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the

meaning of a disputed term." *Phillips*, 415 F.3d at 1315 (quoting *Vitronics*, 90 F.3d at 1582). "The construction that stays true to the claim language and most naturally aligns with the patent's description of the invention [in the specification] will be, in the end, the correct construction." *Id.* at 1316 (quoting *Renishaw PLC v. Marposs Societa' Per Azioni*, 158 F.3d 1243, 1250 (Fed. Cir. 1998)).

III. CONSTRUCTION OF CABILLY II PATENT CLAIMS

A. Technology Background

The Cabilly II Patent generally relates to methods of immunoglobulin (antibody and non-specific immunoglobulin) expression. Cabilly II, Ex. C at 4:53-55.[2] Cabilly II purports to disclose a method for producing such immunoglobulins. The single example in the patent involves transforming an *E. coli* host cell with DNA sequences that code for immunoglobulin polypeptide chains (heavy and light chains). *Id*. at 23:1-25:62. The *E. coli* host cells are then said to express this foreign DNA allowing the heavy and light chains to be produced as separate molecules in that host cell. *Id*. The single example then purports to show isolation and assembly of the two chains into an immunoglobulin outside the host cell. *Id*.

At the time the Cabilly II application was filed, "[r]ecombinant technology was in its infancy, in particular as it related to the expression and assembly of multimeric proteins." Genentech's Response Under 37 CFR 1.550(b) at 35-36 (Reexam Control Nos. 90/007,859 and 90/007,542) (Ex. F). Genentech emphasized that the "state of expression techniques in early April of 1983 was such that a scientist working in this field would have skeptically viewed the idea that coexpression of heavy and light chains was so predictable that it could be described without any mention of a strategy for accomplishing this task." Declaration of Steven Lanier McKnight Under 37 CFR § 1.132 at ¶ 77, dated May 18, 2007 (Reexam Control Nos. 90/007,859 and 90/007,542) (Ex. G). Yet, Cabilly

[2] Patent references are in the form "c:ll-ll," where "c" is the column number in the specification and "ll-ll" is a range of line numbers.

II only discloses a single example of the claimed method in any detail – and this example uses the bacteria *E. coli* as the host cell and a plasmid (vector) which does not become incorporated into the host cell DNA. *See* Ex. C at col. 16-28.[3]

B. Construction of Patent Terms in Dispute

1. "Transformed Host Cell Comprising At Least Two Vectors"

Cabilly II Patent Claims 18 and 20	
"transformed host cell"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
No separate construction needed	**A cell into which foreign DNA has been introduced**
"vector"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction (held by the Court in *MedImmune*)**
No separate construction needed	**A separate DNA molecule that is capable of transporting a DNA segment into another cell**
"transformed host cell comprising at least two vectors"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
Host cell whose heritable DNA has been altered to include foreign DNA from at least two DNA constructs	**A cell into which foreign DNA has been introduced comprising at least two separate DNA molecules that are capable of transporting a DNA segment into another cell**

As an initial matter, Centocor believes that its proposed constructions for the terms "vector" and "transformed host cell" and the phrase "transformed host cell

[3] This is consistent with a Genentech press release issued May 4, 1983, a month after the Cabilly I application was filed. *See* GNE-MED121764 (Ex. H) ("[R]esearchers at Genentech and City of Hope have taken antibody genes from mammalian cells and introduced them into E. coli bacteria using recombinant DNA techniques.").

comprising at least two vectors" track the construction and reasoning provided by the Court in *MedImmune*. Op. at 14-19. Centocor asks the Court (1) to reaffirm its prior construction of the term "vector;" (2) to construe the term "transformed host cell" consistent with Genentech's agreed-upon construction in *MedImmune* (Op. at 7), and (3) to construe the phrase "transformed host cell comprising at least two vectors" as a logical combination of the first two terms. Centocor's proposed constructions conform with both the plain meaning to one of ordinary skill in the art and with usage of the terms in the claims and the Cabilly II specification.

In contrast, Genentech argues against separate construction of the terms "vector" and "transformed host cell" – positions that it has already either conceded or lost – and now attempts to cobble together a new construction for the phrase "transformed host cell comprising at least two vectors." As set forth below, Genentech's proposed construction cannot be correct because it ignores the rules of grammar, the words of the claim, the specification and the understanding of those skilled in the art.

a) Intrinsic Evidence Supports Centocor's Construction

The Cabilly II patent does not define the word "vector." The term must be given the ordinary and customary meaning to one of skill in the art. Since "vector" is a technical term, it is appropriate to consult certain extrinsic evidence, such as a technical dictionary,[4] as the Court did in construing the term in *MedImmune*. There, the Court concluded that a person of ordinary skill in the art would understand the term "vector" to mean a DNA molecule that transfers a DNA segment into a host cell. *See* Op. at 17 (citing King, A Dictionary of Genetics, 3d ed. at 410 (Ex. I) which defines "vector" as "a self-replicating DNA molecule that transfers a DNA segment between host cells; also called a 'vehicle'"). The Court

[4] *Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 996 (Fed. Cir. 2006) ("Because there is no suggestion that the intrinsic evidence defines the [claim] term, . . . one may look to technical dictionaries for assistance in determining that term's meaning to a person of ordinary skill in the art.").

noted that there is a "functional essence" to the term. *Id*. Here, as in *MedImmune*, the dispute is whether a vector remains a vector *after* it becomes integrated into the chromosomal DNA of the host cell.

The Court's prior construction of "vector," which Centocor adopts here, retains the functional essence of the term and is consistent with the use of the term in the patent. For example, the specification distinguishes between the DNA that is introduced into cells to encode immunoglobulins and the vectors capable of effecting the production of such immunoglobulins:

> In other aspects, the invention is directed to DNA which encodes the aforementioned NSIs, antibodies, and portions thereof, ***as well as expression vectors or plasmids capable of effecting the production of such immunoglobulins in suitable host cells***.

Ex. C at 5:30-34 (emphasis added).

Centocor's construction is also supported by the language of the claims. Claim 18 recites a cell "comprising" two vectors, not a cell which once "comprised" two vectors. And other claims distinguish between the DNA sequence which encodes the immunoglobulin chains and the vectors which can contain those sequences. For example, Claim 1 recites a method including the step of transforming a host cell with a first and a second "DNA sequence," while dependent Claims 2 and 3 recite that the "DNA sequence" can be present *in a vector*. This same distinction between "DNA sequence" and "vector" is found in Claim 1 of Cabilly I, which separately recites the "DNA sequence encoding a chimeric immunoglobulin heavy or light chain" and the "expression vector" into which said sequence is inserted. *See* Ex. A at Claim 1.

Centocor's construction is also consistent with the narrow disclosure in Cabilly II. The inventors describe a single example in detail – using *E. coli*, a bacterial host cell – where the "vector" remains separate from the host cell's DNA. *See* Ex. C, 23:1-15. The inventors do not teach how to make or use the alleged invention in a mammalian host cell. Genentech cannot "enlarge what is patented

beyond what the inventor has described as the invention." *Netword*, 242 F.3d at 1352. Genentech's argument that the specification "specifically discusses the use of vectors that were known at the time to integrate into mammalian chromosomal DNA" and that, accordingly, Centocor's definition excludes "embodiments" of the invention is unfounded. At most, the specification provides a laundry list of possibilities, but does not disclose, describe, or teach how to successfully transform mammalian cells. *See Ariad*, Ex. D at *18 ("In the context of this invention, a vague functional description and an invitation for further research does not constitute written disclosure. . . .").

Genentech's insistence that the patent's statements that "if the vector is integrated into the host cell chromosome…" and that expression vectors "must be replicable in host organisms either as episomes or as an integral part of the chromosomal DNA" mandates its broad claim construction is without merit. It is not disputed that some vectors can be integrated into some host cell chromosomes. But that does not mean that the vector ***remains a vector*** once it has been so integrated and has lost its "functional essence." *MedImmune* Op. at 17.

The plain meaning of Claim 18, consistent with the intrinsic evidence, is narrow. It covers a transformed cell that comprises two vectors. It may be the case that, in some instances, immunoglobulin DNA introduced into cells via vectors is incorporated into a cell's chromosomal DNA. But such cells simply are not encompassed by Claim 18. Had Genentech intended to cover instances where the foreign DNA becomes integrated into the host cell's genome, it could have claimed "transforming said single host cell with *a first [and second] DNA sequence*" as it did in Claim 1. *See* Ex. C, Claim 1 (emphasis added).

In arguing that "[n]othing in the specification suggests an intent to limit the scope of the claims" to transformed host cells in which the vectors are not integrated into the host cell DNA (Br. at 12), Genentech misses the point. Centocor is not arguing that there has been a disclaimer or disavowal. Rather,

Centocor's construction is consistent with the plain meaning of the claim language and is supported by the specification. Genentech could have drafted Claim 18 more broadly. It did not do so, and its litigation-induced intent now cannot rewrite the claim.

Genentech grasps at straws by citing to the Axel patent – a patent not cited in the Cabilly II specification itself but cited during the reexamination of Cabilly II more than *twenty years* after Cabilly's effective filing date. (Br. at 14). Even if the relevance of Axel were beyond dispute, it fails to support Genentech's argument. The Axel example to which Genentech refers says nothing more remarkable than that a plasmid (a type of vector) can be incorporated into a cell's DNA and then rescued. It indicates nothing about whether the plasmid sequence is a "vector" before rescue, when it is still a part of the cell's DNA.

b) Genentech's Extrinsic Evidence Cannot Alter the Plain Meaning of the Claim

Genentech's submission of extrinsic evidence in the form of a declaration from Dr. Gething does nothing to alter the plain meaning that the term "vector" would have to one of skill in the art. *See Phillips*, 415 F.3d at 1318 (extrinsic evidence is "less reliable" than the patent); *Vitronics*, 90 F.3d at 1585 (dictionaries "are more objective and reliable guides" than expert testimony).

Dr. Gething's declaration fails to establish that the term "vector" was commonly understood by those in the art to have the meaning inherent in Genentech's construction, namely, that a "vector" remains a "vector" even after it is incorporated into the cell's chromosomal DNA. This is not surprising because she cannot do so. The very reference Dr. Gething relies upon sets forth a number of properties shared by vectors in addition to the ability to transfer DNA to another cell, including: 1) autonomous replication; and 2) easy separation from host cell DNA. *See* Maniatis et al., Molecular Cloning, A Laboratory Manual, 2-3 (Cold Spring Harbor Laboratory Publications, 1982 (Ex. J).

Ignoring this, Dr. Gething instead relies on a tangential example – bacteriophage λ – which, notably, is *not mentioned* at all in the Cabilly II specification. As admitted by Dr. Gething and Genentech, bacteriophage λ loses the ability to transfer DNA to another cell – *i.e.*, ceases to be a "vector" – once it becomes integrated into the host cell's genome. *See* Br. at 6 ("'rescued' plasmid vector retains its functionality post-rescue"); Gething Decl. at ¶¶ 14-15 and 22 (explaining that an integrated plasmid vector must be removed from the host cell genome to regain its functionality as a vector). Further, upon integration, bacteriophage λ also loses the ability to autonomously replicate and to be easily separated from the host cell's DNA.

c) Genentech's Proposed Construction Should Not Be Adopted

Although Genentech agreed in *MedImmune* that it was appropriate to separately construe the term "vector," it now proposes that no construction of the term is needed. This about-face is not surprising. Genentech wishes to avoid ascribing any function to the claim term "vector" by burying it in the broader phrase "transformed host cell comprising at least two vectors." Genentech says this phrase means "a host cell whose heritable DNA has been altered to include foreign DNA from at least two DNA constructs." Thus, Genentech suggests, a "vector" is just a "DNA construct" having "foreign DNA."

But Genentech's tactic must be rejected. Even in the context of the entire phrase, the "functional essence" of a vector cannot be avoided. Under Genentech's proposal, the transformed host cell "has been altered to include foreign DNA from" the vector (*i.e.*, the "DNA construct"). This clearly indicates that it is the vector that is performing the function of altering - of introducing the foreign DNA into the host cell to transform it. If this functional essence is not implied, *i.e.*, if the vector is not the agent of action, then Genentech's proposed construction becomes absurd. It would cover alteration of the host cell by any means whatsoever, not

just by DNA introduced into the host cell by a vector. This, of course, goes far beyond Cabilly's specification.

There is also a problem with Genentech's use of the word "heritable" in its proposed construction. "Heritable DNA" is plainly DNA that is part of the genome of a cell that is passed on from generation to generation. Inclusion of this word cannot be correct as it would exclude the only example provided in the Cabilly II specification – *i.e.*, the use of a plasmid which generally does not become integrated and is not necessarily passed on to progeny.

For all of the reasons explained above, the Court should reaffirm the construction of "vector" which it adopted in *MedImmune*, and should adopt Centocor's construction of "transformed host cell" and of the entire "transformed host cell" phrase.

2. "Immunoglobulin" and "Immunoglobulin Molecule"

Cabilly II Patent Claims 18, 20 and 33	
"immunoglobulin"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
No construction needed	**A tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter chains called light chains, or aggregates of such tetrameric molecules, whether or not specific immunoreactive activity is a property**
"immunoglobulin molecule"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
Tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter polypeptide chains called light chains, or aggregates of such tetrameric molecules, capable of	**A tetrameric molecule consisting of two longer polypeptide chains called heavy chains and two shorter chains called light chains, or aggregates of such tetrameric molecules, whether or not specific**

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binding to a known antigen, whether or not specific immunoreactive activity is a property	**immunoreactive activity is a property**

"Immunoglobulin" and "immunoglobulin molecule" should be construed to mean the same thing. Yet, Genentech will not agree that "immunoglobulin" needs to be construed while at the same time proposing a definition for "immunoglobulin molecule" that is both nonsensical and at odds with the overwhelming intrinsic evidence.

As noted by Genentech, the only difference between the parties' constructions for "immunoglobulin molecule" is that Genentech wishes to depart from the construction it agreed to in *MedImmune* (Op. at 7) and insert "capable of binding to a known antigen" as part of its construction. But Genentech's inclusion of this phrase renders its definition a non sequitur. If, as set forth in the specification, the definition of "immunoglobulin" expressly includes proteins that have "an inability to bind to antigen," then Genentech's attempt to insert "capable of binding to a known antigen" into this definition cannot be correct. *See* Ex. C at 3:3-10.

Genentech's proposed inclusion of the phrase "capable of binding to a known antigen" contradicts the definition of "immunoglobulin" in the specification. The term "immunoglobulin" is broadly defined to "include both antibodies . . . ***and analogous protein substances which lack antigen specificity***" (Ex. C at 1:38-41 (emphasis added)) and the Summary of the Invention explains that "[t]he invention relates to antibodies and to ***non-specific immunoglobulins***." *Id*. at 4:53-55 (emphasis added). Yet, Genentech's proposed construction requires that "immunoglobulins" have the "capacity of binding to a known antigen," thereby excluding those immunoglobulins that lack such capability – *i.e.*, that "lack antigen specificity."

Likewise, the only proteins that the specification defines to have antigen specificity are antibodies. Antibodies are expressly defined as "specific

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immunoglobulin poplypeptides" that "bind specifically to a particular foreign substance" (*Id*. at 1:23, 30-31) and as "tetramers or aggregates thereof which have specific immunoreactive activity, comprising light and heavy chains usually aggregated in the 'Y' configuration" (*Id*. at 6:3-6). In contrast, non-specific immunoglobulins (which are expressly included in the definition of "immunoglobulin") are defined as protein substances which lack antigen specificity and as having ***"an inability to bind to antigen."*** *Id*. at 3:3-10 (emphasis added). Therefore, Genentech's addition of the phrase "capable of binding to a known antigen" directly contradicts the express definition of "immunoglobulin" given in the specification and should be rejected. *See Phillips*, 415 F.3d at 1316 ("the inventor's lexicography governs").

Further, Genentech's effort to read "capable of binding to a known antigen" into the term "immunoglobulin" is contrary to the doctrine of claim differentiation. "[C]laim differentiation takes on relevance in the context of a claim construction that would render additional, or different, language in another independent claim superfluous." *Curtiss-Wright Flow Control Corp. v. Velan, Inc*., 438 F.3d 1374, 1381 (Fed. Cir. 2006); *see also Phillips*, 415 F.3d at 1324-25. Independent Claim 21 expressly further limits "immunoglobulin" with the exact term Genentech wishes to read into the other independent claims. It recites "recovering the immunoglobulin from the host cell culture, said immunoglobulin being capable of binding to a known antigen." If "immunoglobulin" were invariably required to be "capable of binding to a known antigen," then the quoted language in Claim 21 would be superfluous.

Genentech supports its construction based on statements that it made to the PTO as part of the reexamination proceeding. *See* Br. at 17-18. To overcome years of prior art rejections, Genentech argued that an "immunoglobulin molecule" must be "capable of binding to a known antigen." *See* Sernel Decl., Ex. L, Feb. 23, 2009 NIRC, 3. And, despite the fact that that definition is directly contrary to the

express definitions in the specification, the PTO bought Genentech's argument and relied on that faulty definition of "immunoglobulin molecule" as one of the reasons for reversing two years of rejections of the Cabilly II claims in the reexamination. *See id*. But the fact that the PTO fell for Genentech's smoke-and-mirrors argument cannot alter the plain meaning of these terms as set forth in the specification. "Although the prosecution history can and should be used to understand the language used in the claims, it cannot enlarge, diminish or vary the limitations in the claims." *Rhodia Chimie v. PPG Indus.*, 402 F.3d 1371, 1379 (Fed. Cir. 2005) (internal citations omitted); *Rosen Entm't Sys. v. Eiger Vision*, 343 F. Supp. 2d 908, 914-15 (C.D. Cal. 2004). As Genentech is improperly seeking to vary the "immunoglobulin molecule" limitation, its proposed construction should be dismissed.

3. "Produced As Separate Molecules in a Single Host Cell"

Cabilly II Patent Claim 33	
"produced as separate molecules in a single host cell"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
No construction needed	**The heavy and light chains of the immunoglobulin molecule are produced as separate molecules while in the host cell**

The heart of the dispute between the parties on the construction of "produced as separate molecules in a single host cell" boils down to a dispute over the scope of what was actually invented by Cabilly. This Court recognized that, without this limitation, the validity of Claim 33 as it was previously construed is suspect. Op. at 10 n.4, 12 and 14 ("techniques sufficient to induce *in vivo* assembly were . . . at a minimum, not taught by the '415 Patent – especially with respect to mammalian cells").[5] Centocor's proposed construction properly limits

[5] Genentech also argues that "Centocor has not offered any reason why this

the scope of Claim 33 to the process disclosed, described and taught in the specification – immunoglobulin chains that are recombined *outside* the host cell where they have been produced.

Centocor recognizes that the Court previously declined to adopt the construction Centocor propounds on the ground that the claim language is "unambiguous in its silence about the fate of the immunoglobulin heavy and immunoglobulin light chains after their independent expression." Op. at 13. This, however, is one of the admittedly rare cases where it is appropriate to adopt a narrow claim construction because of the narrow disclosure in the specification. Centocor urges the Court to reconsider its previous construction based on evidence, case law and argument that it did not consider in *MedImmune*.

a) The Preamble is a Limitation That Requires the Production of an Immunoglobulin

As an initial matter, the parties have agreed that the preamble of Claim 33 of Cabilly II – "a process for producing an immunoglobulin molecule or an immunologically functional immunoglobulin fragment comprising at least the variable domains of the immunoglobulin heavy and light chains, in a single host cell" – is a claim limitation. *See* Ex. K. The preamble is the only portion of claim 33 that refers to "producing an immunoglobulin" and reflects that the claim requires more than just the expression of heavy and light chains in a host cell. *See* Ex. C, Abstract ("The invention relates to a process for producing an immunoglobulin or an immunologically functional immunoglobulin fragment . . . "); *Id*. at 4:53-55. Claim 33 requires the *production of an immunoglobulin or an immunologically functional immunoglobulin fragment* and this distinction is a key

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phrase requires construction." (Br. at 21). However, as recognized by the Federal Circuit, there is no threshold requirement for the identification of claim terms for construction. The purpose of claim construction simply is to construe terms that may be unfamiliar or confusing to the jury or and to resolve disputes as to the meaning or technical scope of terms. *See United States Surgical Corp. v. Ethicon, Inc.*, 103 F.3d 1554, 1568 (Fed. Cir. 1997).

consideration in construing the disputed term.

b) "Produced As Separate Molecules In A Single Host Cell" Should Not Be Construed More Broadly Than the Disclosure in the Specification

The closest precedent on this issue is *Biogen, Inc. v. Berlex Labs., Inc.*, 318 F.3d 1132, 1140 (Fed. Cir. 2003). There the claim recited, *inter alia*, a method for production of human interferon in a CHO cell comprising growing a CHO cell having incorporated therein "a DNA construct." The claim construction issue was whether the claim language was limited to use of a *single* DNA construct. Biogen pointed out that the entire specification was directed solely to an invention where a single DNA construct was used to carry genes into the CHO cell. It argued that, if Berlex's construction allowing for more than a single DNA construct were adopted, the claims would be invalid for lack of an adequate written description. Berlex argued that a statement in the Biogen patent that "[a]ny approach may be used to introduce the cloned DNA into CHO cells and to select and grow the transformed cells for expression of the protein," showed that the invention was not limited to any specific method of introduction of interferon DNA and that other methods of co-transformation were known in the art. But those statements did not save the day. The district court found that the patent discussed only the invention where a single DNA construct was used and held that the claim was so limited, and the Federal Circuit affirmed. *Id*. *See also Netword,* 242 F.3d at 1352 ("Although the specification need not present every embodiment or permutation of the invention and the claims are not limited to the preferred embodiment of the invention, neither do the claims enlarge what is patented beyond what the inventor has described as the invention.") (citations omitted)

As in *Biogen*, the *only* method disclosed in the Cabilly II specification for the assembly of the heavy and light chains is one that occurs *outside of the host cell*. *See* Ex. C at 12: 50-63; 12:66 –13:52; 25:7-50 (disclosing experiment where heavy and light chains were reconstituted outside the host cells after the host cells

were lysed); *MedImmune* Op. at 10 n.4; original claims 42-50 (Ex. L) (method restricted to recovery outside the host cell). *In vivo* assembly is not taught by the Cabilly II patent. *See MedImmune* Op. at 10 n.4.

Further, the Cabilly II specification specifically refers to "the invention" as producing heavy and light chains in isolation from one another, and to advantages of that aspect of the invention:

> The ability of the ***method of the invention*** to produce heavy and light chains or portions thereof, ***in isolation from each other*** offers the opportunity to create unique and unprecedented assemblies of immunoglobulins, Fab regions, and univalent antibodies. Such preparations ***require the use of techniques to reassemble isolated chains***.

(Ex. C at 12:58-63, emphasis added).

The only statement in the Cabilly II specification on which Genentech can hang its argument is the speculative statement that recovery of reconstituted antibody "***might be possible*** in vivo in a microorganism which secretes the IgG chains out of the reducing environment of the cytoplasm." (*Id*. at 12:52-55). But this conjecture does not inform a person of skill in the art that such *in vivo* reconstitution is part of the invention and certainly is not sufficient to describe how to carry out such *in vivo* reconstitution. Just as the catch-all statement in the *Biogen* case did not save the claims from a scope limited by the breadth of the description in the patent, this speculative statement in the Cabilly II patent cannot justify the broad construction of Claim 33 sought by Genentech. *See also Ariad*, Ex. D at *18-19.

Cabilly did not invent, disclose or describe an invention in which heavy and light chains expressed within a cell are combined in the cell, and is not entitled to a claim construction which is broader than his invention.[6]

[6] Centocor agrees that the term "in a single host cell" does not need separate construction.

c) Claim Differentiation Does Not Preclude Centocor's Proposed Construction

Genentech also argues (and this Court previously found persuasive) that the doctrine of claim differentiation precludes the adoption of Centocor's proposed construction. However, claim differentiation can not be used to "broaden claims beyond their correct scope." *Curtiss-Wright*, 438 F.3d at 1381. Although dependent claims 9 and 10 (not at issue here) attempt to further define the process of producing an immunoglobulin molecule, the presumption that these claims have a different scope than independent claim 1 is overcome by the limiting disclosure of the written description.[7] *See Fantasy Sports Properties, Inc. v. Sportsline.com, Inc.*, 287 F.3d 1108, 1115-15 (Fed. Cir. 2002) (holding that independent and dependent claims have the same scope based on written description and prosecution history). Thus, Genentech cannot use the doctrine of claim differentiation to capture subject matter that it neither invented nor described. *See id*. *See generally Netword*, 242 F.3d at 1352 (The claims cannot "enlarge what is patented beyond what the inventor has described as the invention.").

In an analogous context, the Federal Circuit has similarly held that the language of a dependent claim may not be used improperly to broaden the scope of an independent claim. *See North Am. Vaccine, Inc. v. American Cyanamid Co.*, 7 F.3d 1571, 1577 (Fed. Cir. 1993) ("The dependent claim tail cannot wag the independent claim dog."). "While it is true that dependent claims can aid in interpreting the scope of claims from which they depend, they are only an aid to interpretation and are not conclusive." *Id*. Here dependent claim 9 cannot be used to advocate for a construction that covers "that which is neither described nor enabled in the patent." *See id*. In view of these cases, Genentech's claim differentiation argument is unpersuasive.

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[7] This is not the case for the construction of "immunoglobulin" where Centocor uses the doctrine of claim differentiation consistently with the express definition of "immunoglobulin" in the specification.

4. The Court Should Adopt Centocor's Proposed Construction for "Variable Domain"

Cabilly II Patent Claims 18, 20 and 33	
"variable domain"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
No construction needed	**The N-terminal end of the heavy and light chains up to the beginning of the constant domain**

Centocor believes that the term "variable domain" is not readily understandable on its face by a jury, and thus should be construed. Genentech previously agreed to this very construction in *MedImmune* and has conceded here that it will accept Centocor's proposed construction. *See* Br. at 1 n.2.

5. The Parties Agree On The Construction of "Immunologically Functional Immunoglobulin Fragment"

Cabilly II Patent Claim 33 Agreed-Upon Construction
"immunologically functional immunoglobulin fragment"
a portion of an immunoglobulin molecule that is capable of binding to a known antigen

There is no dispute between the parties on the construction of "immunologically functional immunoglobulin fragment" and accordingly, Centocor asks the Court to adopt the agreed-upon construction set forth above. Centocor notes – in contrast to its proposed construction for "immunoglobulin" above – that here it has no objection to the inclusion of the phrase "capable of binding to a known antigen" as the claim term itself requires that the fragment be "immunologically functional."

IV. CONSTRUCTION OF THE 335 PATENT CLAIMS

A. Background

The 335 Patent is related to a method of antibody purification using cation exchange chromatography. Contrary to the implication in Genentech's brief, the named inventors on the 335 Patent did not invent the concept of purifying antibodies in commercial quantities. Br. at 2-3, 6. Indeed, the 335 patent specification refers to "different chromatography techniques" already then known. Ex. E at 1:18-2:12. Nor did the named inventors discover cation exchange chromatography. The specification candidly admits that this process was "commonly used" at the time. *Id*. at 1:66-67; *see also* 17:30-31.

What the 335 Patent in fact narrowly claims is the use of a specific ratio of antibody to resin for loading antibody into a cation exchange chromatography column. The patent refers to this ratio as the "load density" or the "load," and measures it as milligrams (mg) of antibody per milliliter (mL) of resin. *Id*. at 22:2-4, 24:20-24, 24:42-49, and 24:61-67. Each of the 335 Patent claims requires an almost identical load density – either "from 20 mg to 35 mg" (asserted claim 7) or "from about 20 mg to about 35 mg" (asserted claims 1, 2, and 3). The difference in this claim language arises not from the numerical range, but from the fact that three of the asserted claims preface the claimed range with "about." Centocor seeks construction of this term.

B. "About"

335 Patent	
"about"	
Genentech and City of Hope's Proposed Construction	**Centocor's Proposed Construction**
No construction needed	**Within the range of experimental error that occurs in any experiment**

Contrary to Genentech's position, the word "about" is not a "simple, non-technical word" with a "commonly understood meaning." Br. at 23-24. Far from it,

The Federal Circuit has repeatedly explained that "about" "does not have a universal meaning in patent claims, and [its] meaning depends on the technological facts of the particular case." *Cohesive Techs. v. Waters Corp.*, 543 F.3d 1351, 1368 (Fed. Cir. 2008) (emphasis added), *quoting Pall Corp. v. Micron Separations, Inc.*, 66 F.3d 1211, 1217 (Fed. Cir. 1995). "About" "must be interpreted in its technological and stylistic context," which includes an examination of the patent specification and prosecution history to determine "the purpose of the limitation in the claimed invention." *Cohesive*, 543 F.3d at 1368, 1370 n.3; *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs.*, 476 F.3d 1321, 1326-27 (Fed. Cir. 2007).

Genentech engages in no such analysis of the intrinsic evidence, insisting instead that "about" needs no construction or, in any event, should be construed to mean nothing more definite than "approximately," an equally amorphous word. Br. at 23-24. Genentech's non-construction would give it free rein to deviate from the upper 35 mg/mL and lower 20 mg/mL bounds that the 335 Patent carefully delineates. But a person of ordinary skill in the art reviewing the intrinsic evidence would come to a different conclusion: Any variability around the 20 to 35 mg/mL range introduced by "about" is meant to be narrow. "About" provides the flexibility necessary to account for a range of experimental error, not a license to erase defined claim boundaries.

The heart of this intrinsic evidence, which Genentech ignores, is the specification's discussion of the experiments that led to the claimed load density range. In the patent's only example, six chromatography experiments were run with "human IgG rhuMAB HER2" antibody at six different "load densities of 15, 20, 25, 30, 35, and 40 mg" per mL. Ex. E at 21:12, 22:2-5. The named inventors then did a "study" of the experiments to arrive at the 20 to 35 mg/mL load range. *Id*. at 24:55-56. 35 mg/mL was selected as the upper bound because loads greater than it produced a lower, unacceptable antibody yield: "The quantity of rhuMAb HER2 recovered, however, is reduced by approximately 10% when the resin is

loaded with greater than 35 mg/mL." *Id*. at 24:58-61. At the other end, 20 mg/mL was chosen as the lower bound because loads below it required the use of greater volumes of buffer wash fluid, making cation exchange chromatography less economical. *Id*. at 24:66-67. For these reasons, "20 mg/mL" was selected as the "minimal load," and "35 mg/mL" as the "maximum load":

- "due to the substantial increase in the 70 mM NaCl wash volume requirement, it is recommended that 20 mg/mL be set as the minimal load for manufacture of rhuMAb HER2" *Id*. at 24:66-67 (emphasis added)
- "For consistent yields it is recommended that 35 mg/mL be set as the maximum load for manufacture of rhuMAb HER2" *Id*. at 24:61-63 (emphasis added)

This disclosure is compelling intrinsic evidence that any variability around the upper and lower load density bounds was meant to be small. In explaining the testing and selection that led to the claimed range, the specification focuses on "20 mg/mL" precisely and "35 mg/mL" precisely – not "about 20" or "about 35." Indeed, the specification notes that poorer yields resulted at loads "greater than 35 mg/mL" – not "about 35 mg/mL." *Id*. at 24:58-61 (emphasis added)

The use of the "about" modifier in the claims may introduce some variability around these defined boundaries, but it should not permit them to be expanded in the undefined and arbitrary way that Genentech proposes. The Federal Circuit's recent *Ortho-McNeil* decision addressed a similar "about" limitation in a claim to a pharmaceutical composition requiring two ingredients to be present in an "about 1:5" ratio. *Ortho-McNeil*, 476 F.3d at 1327. The Court held, based on the specification's discussion of the experimental data points that led to this ratio, that "about 1:5" was intended to be "narrow" and only "was meant to encompass compositions very close to that ratio." *Id.* The specification showed experiments at other ratios like 1:1, 1:3, and 1:5.7, and in finding a narrow range of variability for "about 1:5," the Federal Circuit believed it persuasive that the inventors "could easily have claimed" these other ratios "but they did not." *Id.* at 1327-28.[8]

[8] *See also Cohesive*, 543 F.3d at 1369 (holding that a limitation requiring

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As in *Ortho-McNeil*, the 335 Patent's named inventors disclosed that they had conducted a series of experiments at varying ratios, and had rejected some of the tested ratios in favor of the ones specifically claimed. Thus, as in *Ortho-McNeil*, the specification's disclosure clearly indicates that any deviation from the selected and claimed 20 to 35 mg/mL range was meant to be "narrow" and "to encompass [loads] very close to that ratio." *Ortho-McNeil*, 476 F.3d at 1327.

This narrowness is further highlighted by the prosecution history, about which Genentech is also silent. Genentech's counsel made "clear and unmistakable disavowal[s] of scope during prosecution" whenever the examiner suggested that "about" could be read as materially expanding the claimed range. *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374 (Fed. Cir. 2008). For the upper 35 mg/mL boundary, Genentech's counsel expressly disavowed any expansion of that ratio to reach 40 mg/mL (one of the loads tested but not included in the claimed range): "the claimed range of about 20-35 mg/mL would exclude 40 mg/mL at the upper end of the range." Ex. M at GENE-CEN 000451 (emphasis added). Likewise, for the lower boundary, when the examiner suggested that a ratio of 8 mg/mL might fall within the "about 20 mg/mL" limitation, Genentech dismissed the notion as unthinkable: "8 mg/mL is clearly not 'about 20 mg/mL.'" *Id.* (emphasis in original).

The most natural reading of "about" in the technological context of the 335 Patent is the construction that Centocor proposes: "within the range of experimental error that occurs within any measurement." The named inventors based their claimed load density range on the results of experimental chromatography runs done at specific loads. Ex. E at 22:2-4. But the technological reality is that in any given experiment, there is uncertainty in the

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particles to have diameters of "about 30 [mu] m" could not be construed to cover particles with a 20 [mu] m diameter, because the specification disclosed that the desired performance "'could not be attained with particles' of 20 [mu] m diameters").

measurements used. Modifying the selected boundaries with the term "about" would account for this error. This would be consistent with a number of claim construction cases recognizing that "about" is intended to account for such experimental or measurement error. *See Hybritech, Inc. v. Abbott Laboratories*, 849 F.2d 1446, 1455 (Fed. Cir. 1988) (the limitation "at least about 10<8> liters/mole" construed as encompassing "two- to three-fold measurement errors inherent in affinity measurements"); *Ortho-McNeil*, 476 F.3d at 1328 ("about 1:5" ratio construed to encompass a wider numerical range based on the patent's disclosure of "statistical variability in the measured responses for each ratio"); *Eli Lilly & Co. v. Teva Pharms. USA*, 1:06-cv-1017-SEB-JMS, 2008 U.S. Dist. LEXIS 45719, at *15-16 (S.D. Ind. June 11, 2008) ("Lilly's patents use the word 'about' to reflect the range of measurement variability to be reasonably expected").

Centocor's proposed construction for "about" comports with the natural understanding of that modifier as providing for a range of experimental error. This proposed construction would allow for later expert testimony, from both parties, addressing what the proper "range of experimental error" would be in the field of antibody purification by cation exchange chromatography. Moreover, Centocor's proposed construction accounts for all of the disclaimers and language in the 335 Patent and prosecution history highlighting the narrowness of any variability introduced by "about." Genentech's proposed non-construction turns a blind eye to this compelling intrinsic evidence.

Neither the 335 Patent's specification nor its prosecution history suggest or support any other interpretation. Genentech's attempt to leave "about" undefined and amorphous should be rejected.

V. CONCLUSION

For all of the above reasons, Centocor respectfully requests that its proposed claim constructions be adopted.

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